

WHAT IS CLAIMED IS:

1. A conjugate of uricase that retains at least about 75% of the uricolytic activity of unconjugated uricase and is substantially non-immunogenic, comprising a purified uricase comprising subunits in which each subunit of the uricase is covalently linked to an average of 2 to 10 strands of PEG, wherein each molecule of PEG has a molecular weight between about 5 kDa and 100 kDa.
2. The conjugate of Claim 1, wherein the uricase is mammalian uricase.
3. The conjugate of Claim 2, wherein the uricase is porcine liver, bovine liver or ovine liver uricase.
4. The conjugate of Claim 1, wherein the uricase is recombinant.
5. The conjugate of Claim 4, wherein the uricase has substantially the sequence of porcine, bovine, ovine or baboon liver uricase.
6. The conjugate of Claim 4, wherein the uricase is chimeric.
7. The conjugate of Claim 6, wherein the chimeric uricase contains portions of porcine liver and baboon liver uricase.
8. The conjugate of Claim 7, wherein the chimeric uricase is PBC uricase.
9. The conjugate of Claim 7, wherein the chimeric uricase is PKS uricase.
10. The conjugate of Claim 4, wherein the uricase has substantially the sequence of baboon liver uricase in which tyrosine 97 has been replaced by histidine.
11. The conjugate of Claim 4, wherein the uricase comprises an amino terminal and a carboxyl terminal, and wherein the uricase is truncated at one terminal or both terminals.
12. The conjugate of Claim 1, wherein the uricase is a fungal or microbial uricase.
13. The conjugate of Claim 12, wherein the fungal or microbial uricase is isolated from *Aspergillus flavus*, *Arthrobacter globiformis* or *Candida utilis*, or is a recombinant enzyme having substantially the sequence of one of those uricases.
14. The conjugate of Claim 1, wherein the uricase is an invertebrate uricase.
15. The conjugate of Claim 14, wherein the invertebrate uricase is isolated from *Drosophila melanogaster* or *Drosophila pseudoobscura*, or is a recombinant enzyme having substantially the sequence of one of those uricases.
16. The conjugate of Claim 1, wherein the uricase is a plant uricase.
17. The conjugate of Claim 16, wherein the plant uricase is isolated from root nodules of *Glycine max* or is a recombinant enzyme having substantially the sequence of that uricase.

18. The conjugate of Claim 1, wherein the PEG has an average molecular weight between about 10 kDa and 60 kDa.

19. The conjugate of Claim 18, wherein the PEG has an average molecular weight between about 20 kDa and 40 kDa.

5 20. The conjugate of Claim 1, wherein the average number of covalently coupled strands of PEG is 3 to 8 strands per uricase subunit.

21. The conjugate of Claim 20, wherein the average number of covalently coupled strands of PEG is 4 to 6 strands per uricase subunit.

10 22. The conjugate of Claim 1, wherein the uricase is tetrameric.

23. The conjugate of Claim 1, wherein the strands of PEG are covalently coupled to uricase via linkages selected from the group consisting of urethane linkages, secondary amine linkages, and amide linkages.

24. The conjugate of Claim 1, wherein the PEG is linear.

25. The conjugate of Claim 1, wherein the PEG is branched.

15 26. A pharmaceutical composition for lowering uric acid levels in a body fluid or tissue, comprising the conjugate of Claim 1 and a pharmaceutically acceptable carrier.

27. The pharmaceutical composition of Claim 26, wherein said composition is stabilized by lyophilization and dissolves promptly upon reconstitution to provide solutions suitable for parenteral administration.

20 28. A method for lowering elevated uric acid levels in a body fluid or tissue of a mammal, comprising the step of administering to said mammal an effective uric acid-lowering amount of PEG-uricase, said PEG-uricase comprising a purified uricase comprising at least two subunits in which each subunit is covalently linked to an average of 2 to 10 strands of PEG, wherein each molecule of PEG has a molecular weight between about 5 kDa and 100 kDa, in a pharmaceutically acceptable carrier.

25 29. The method of Claim 28, wherein said mammal is a human.

30. The method of Claim 28, wherein the administering step is selected from the group consisting of injections by intravenous, intradermal, subcutaneous, intramuscular and intraperitoneal routes or inhalation of an aerosolized formulation.

30 31. The method of Claim 28, wherein said elevated uric acid levels are associated with a condition selected from the group consisting of gout, tophi, renal insufficiency, organ transplantation and malignant disease.

32. The method of Claim 28, wherein the PEG is linear.
33. The method of Claim 28, wherein the PEG is branched.
34. A method for isolating a tetrameric form of uricase from a solution of uricase, said solution comprising tetrameric uricase and uricase aggregates, comprising the steps of:
 - 5 applying said solution to at least one separation column at a pH between about 9 and 10.5; and
 - recovering from said column one or more fractions that contain isolated tetrameric uricase, wherein said one or more fractions are substantially free of uricase aggregates.
35. The method of Claim 34, wherein said solution of said uricase is applied to said column 10 at a pH of 10.2.
36. The method of Claim 34, wherein said separation is based on a property selected from the group consisting of ion exchange and size exclusion.
37. The method of Claim 34, further comprising the step of analyzing said fractions to determine at least one property selected from the group consisting of presence of said tetrameric 15 uricase and absence of uricase aggregates.
38. The method of Claim 37, wherein said analyzing step comprises at least one analysis selected from the group consisting of chromatography, centrifugation, light scattering and electrophoresis.
39. The method of Claim 38, wherein said chromatography is high performance liquid 20 chromatography.
40. The method of Claim 34, wherein said isolated tetrameric uricase contains less than about 10% uricase aggregates.
41. An isolated tetrameric uricase produced by the method of Claim 34.

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